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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Resting state fMRI and analyses of intrinsic functional networks are powerful tools for characterizing functional networks in pediatric and clinical populations. In control infants and toddlers who are scanned during natural sleep, fMRI has been used to characterize the typical development of intrinsic functional networks during resting states. Autism spectrum disorder (ASD) begins prenatal, and early maldevelopment is present in many sites and systems that mediate intrinsic network function. These networks have been little studied in ASD infants and toddlers. Our project appears to be among the first to do so. In this project N=96 ASD and typical infants and toddlers were studied; analyses of intrinsic networks provided evidence of significant and widespread disruptions in functional networks in ASD that are crucial for social, communication, cognitive, attention and salience functions. These are among the first-ever studies of the intrinsic connectivity patterns in infants and toddlers with ASD at the age of first clinical identification. The knowledge provided by our studies in combination with those of Co-PIs Dr. Fox and Dr. Glahn could open new avenues of basic genomic and animal model research that elucidate the biological bases of aberrant intrinsic network development in ASD and may identify early diagnostic, prognostic and treatment-responsiveness biomarkers of ASD.

15. SUBJECT TERMS

Nothing listed

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1. INTRODUCTION

Resting state functional magnetic resonance imaging (rsFMRI) and the analysis of intrinsic functional connectivity are powerful tools for characterizing functional networks in pediatric and clinical populations. In infants and toddlers who are scanned during natural sleep, rsFMRI has been used to characterize the development of intrinsic functional networks during resting states [1-6]. Not only has this body of work revealed that disruptions in early development, such as pre-term birth, can result in measurable changes in these intrinsic networks [1,4], but it has also shown, perhaps surprisingly, that the majority of them are fully or mostly formed by age 2 [6-9]. Furthermore, intrinsic *sensory* networks seem to emerge earliest and present adult-like topology by birth, while intrinsic networks involved in higher order functions merge later. Specifically, the *default mode network* (DMN) and the *dorsal attention network* (DAN) emerge by age 1 and the *salience and fronto-parietal control networks* emerge by age 2 [8,9]. Moreover, by age 1 year, the DMN and DAN (also known as the task-negative and task-positive networks due to their relative deactivation and activation while performing a cognitive task) demonstrate their characteristic anticorrelated relationship and these anticorrelations increase in the second year of life Gao, 2013 #8568}. After infancy and toddlerhood, these various networks become further refined and the relationships between them change.

New cellular, molecular and genomic evidence indicates autism spectrum disorder (ASD) begins prenatally, most likely by or before the late second trimester [10-15] as do ASD animal model studies [16-18]. Prenatal maldevelopment in ASD involves dorsolateral and mesial prefrontal cortex, temporal cortex, amygdala and cerebellum [19]. These are among the key structures that mediate the normal development and function of the higher-order intrinsic networks described above, such as DMN and DAN. New diffusion tensor imaging (DTI) and activation-based fMRI from the Courchesne lab report the presence of structural and functional abnormality in these structures by ages 1 to 2 years in ASD [20-25]. Therefore, we hypothesize that the early neural maldevelopment of these key structures disrupts the normal formation and function of these important higher-order intrinsic networks, which underlie social, communication, cognitive and attention functions. Remarkably, these networks have not been well studied in ASD at the earliest ages. This is a major gap in basic and clinical knowledge. Such knowledge could open new avenues of basic genomic and animal model research that can elucidate the developmental neural biological bases of ASD and early clinical diagnostic and prognostic biomarker research.

The Courchesne lab has gathered the largest existent sample of resting state fMRI data from ASD infants and toddlers. With this invaluable resource, we will identify early developmental patterns of intrinsic functional network abnormalities in ASD infants and toddlers as compared with typically developing (TD) controls. Because the Courchesne lab routinely also collects longitudinal clinical data from all infants and toddlers, analyses will also investigate whether there may be subtypes of abnormal intrinsic connectivity patterns based on early clinical presentation and/or on later clinical outcome, such as language and social outcome by ages 3 to 4 years.

2. KEYWORDS

Autism spectrum disorder, ASD, early brain development, intrinsic functional brain networks, fMRI, infants, toddlers, clinical presentation, clinical outcome, genomic, biomarker

3. ACCOMPLISHMENTS

a. **What were the major goals of the UC San Diego Site?**

Major Task 1 was to submit and obtain HRPO approval; this was accomplished ahead of the Milestone #1 schedule by October 13, 2014.

Major Task 2 was to obtain staffing and this Milestone #2 was accomplished. We engaged Dr. Lisa Eyler (see **Section 7. Participants**, below) in the project at 10% effort by October of 2104; she is a junior faculty in Psychiatry at UC San Diego and expert in fMRI methodology and in autism neurofunctional imaging. Next, we recruited and trained (see **subsection c.**, below, as well as **Section 7. Participants**, below) a UCSD graduate student in fMRI resting state methodologies used for analyses of intrinsic functional networks. Her training was accomplished by Spring 2015.

Specific Aim 2 (UC San Diego Site):

i. Major Task 1: ASD MRI Data Pre-Processing (Subtasks 1 and 2). Subtask 1 was to preprocess all MRI structural data and this was completed using FreeSurfer 5.1. Subtask 2 was to preprocess all resting state fMRI data and has been completed for N=96 ASD and TD subjects whose data is in our first set of intrinsic connectivity analyses (see below). Milestone #1 under this Task 1 (data pre-processing of this n=96 subject fMRI and MRI dataset) was accomplished by Spring 2015. We anticipate being able to process in the coming year a second set of ASD and control subjects that would enable replication and validation analyses with no change to the total original budget but which would require additional time (see section **5. Changes**).

ii. <u>Major Task 2: Intrinsic Connectivity Analyses in ASD and TD Subjects</u>. This Milestone #2 is to be completed by early in Year 2 of the project. By project month 11 we completed the intrinsic connectivity analyses in ASD and TD subjects described **next in subsection b**., below.

b. What was accomplished under these goals at the UC San Diego Site?

Major activities were select from our larger database of infants and toddlers (>1,300 individuals) a subset of carefully matched ASD infants and toddlers who had both high quality structural MRI and resting state fMRI data, were identified and imaged at young ages and had longitudinal clinical diagnostic and psychometric tracking and follow-up testing to confirm diagnoses and clinical outcome. Further, selected subjects needed to be age and gender matched to increase statistical power.

For our initial resting state fMRI analyses of intrinsic networks, we used data from 48 ASD and 48 TD infants and toddlers. The following sections describe design and results of these first studies aiming to identify aberrant intrinsic connectivity patterns in ASD at the age of first clinical detection:

<u>Subjects</u>

Subjects were 48 ASD and 48 TD one-to-one gender- and age- (+/- 3.5months) matched infants and toddlers. Each group contained 19/48 (40%) females. The ages ranged from 13 to 45 months with a mean of 30 months (SD=9) in All subjects received a battery of psychological tests and final diagnoses were confirmed by licensed clinical psychologists at the Courchesne lab.

<u>MRI Structural Imaging</u>

To obtain multiple neuroanatomical surface and volumetric measures, all subjects received a T1-weighted anatomical scan with 1x1x1mm isotropic voxels. Our processing pipeline produces multiple detailed anatomic measures (e.g., regional cortical gradients of gray matter (GM), surface area (SA), gyrification index (GI), thickness and volumes of white matter (WM), volumes of cerebellar GM and WM, GM volumes of amygdala and striatum). It uses a combination of FSL, BrainVisa and FreeSurfer for accurate measurement of brains as young as 12 months and allows for easy identification of errors due to automated large batch processing. We used FSL's FLIRT to register the brains to a custom template consisting of an infant brain that has been registered into MNI space. GM, WM and CSF were segmented with FSL's FAST algorithm. We modified the algorithm to use partial volumes of voxels rather than neighboring voxels in order to accurately segment the small white matter tracts in temporal lobe and partial volumes of sulcal CSF at this early stage in brain development when white matter tracts are not yet robust enough to be picked up by traditional segmentation algorithms. A Matlab algorithm, adaptive disconnection, then parcellated the brain into cerebral hemispheres, cerebellar hemispheres, and brainstem. Cerebral and cerebellar hemispheres and subcortical structures entered separate processing streams. Subcortical structures were automatically identified and quantified in FreeSurfer. Cerebral hemispheres and sulci were reconstructed in BrainVisa and recombined with the original FSL segmentation to reconstruct the original surface morphology of each child's cortex. Each subject's individual anatomy was used to identify cortical subregions for measurement, allowing for measurement of unusual folding and hypergyrification. The method was optimized for measurement of surface area within the tight sulci of the infant brain and can be applied to unusually large as well as unusually small cortex.

<u>Resting State Imaging</u>

Our highly successful natural sleep neuroimaging procedure was used to acquire fMRI and MRI data on a GE 1.5T scanner at UC San Diego RIL Center. Key features of the procedure include mild sleep deprivation on the preceding night, vigorous physical activity on scan day, and scans that commence one hour past normal bedtime. Once asleep in the scan room weighted blankets and gradual habituation to scanner noises were used to promote continued sleep. Scanning began about 10 minutes after sleep onset and lasted approximately 30 minutes. In the first published sleep MRI-EEG study of toddlers and young children, Drs. Fox, Courchesne and Manning demonstrated that children go into Stage 3 slow wave sleep within the first 5-10 minutes after nighttime sleep onset, and stay in that stage for about 45 min, thus allowing ample time for data collection while in within a single sleep stage. Resting state fMRI was conducted with a 1.5T scanner using a T2*-weighted EPI sequence with the following parameters: TR = 2.5 s, TE = 30 msec, voxel size of 4 x 4 x 4 mm. The scan lasted for 6 minutes and 25 seconds in the absence of any stimulation, and 154 volumes were acquired.

<u>Data Analysis</u>

First, separate scripts were run for subjects who received additional field mapping scans (60 of the 96 subjects) and those who did not (36/96) in order to reorder raw DICOM files from the functional scans and condense them into BRIK and HEAD files. For the subjects with field map scans, these were used to correct for geometric distortions. During this pre-processing stage, motion correction was done to the middle reference volume, which was confirmed to not have been an outlier in any of our subjects, and a list of motion outliers was created.

Functional data and anatomical data were further pre-processed using modified versions of scripts from the 1000 Functional Connectome Project (SOURCE). Pre-processing steps were conducted primarily in AFNI, but spatial smoothing, grand-mean scaling, binary mask creation, and registrations were conducted in FSL 5.0. First, anatomical scans were deobliqued, oriented to RPI space, and skull-stripped. Second, functional scans were processed by dropping the first three TRs, deobliquing, orienting to RPI space, skull-stripping, spatial smoothing using a 6mm FWHM Gaussian kernel, grand mean scaled to 1000, temporally filtered using a 0.1-0.005Hz bandpass filter, and removed of linear and quadratic trends. This allowed for the creation of binary functional masks. For functional to anatomical registration, the 8th volume from the functional scan was using to automatically register the functional to the anatomical scan using FSL's FLIRT. For registration into MNI standard space, FLIRT was used to generate an initial transformation estimate, and this affine estimate was used by FSL's FNIRT to non-linearly register anatomical and functional scans into standard space. Following segmentation of the anatomical scan into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF), these same transformation matrices were used to linearly register cerebrospinal fluid (CSF) and white matter (WM) to functional space, nonlinearly register them to the MNI standard space, find overlap with tissue priors (provided with the 1000 Functional Connectome scripts), return to functional space, threshold and binarize these maps and mask them by the previously-made functional mask. Next, reference functions of global functional mean, CSF mean and WM mean signals were made by applying the relevant masks to the preprocessed functional timeseries. A general linear model (GLM) was run on the functional timeseries (excluding the first three TRs and the volumes with motion outliers) to get rid of the nuisance variables (six motion parameters, CSF and WM mean signals) and create maps of the residuals. These maps were then demeaned, added to 100 and nonlinearly registered to standard MNI space.

Next, a seed-based approach was used to calculate, for each subject, the correlation between the average timecourse within a seed with every other voxel in the brain. To do this, three seeds [26] from each of the intrinsic functional networks of interest, namely DMN, DAN and Salience networks, were first nonlinearly registered into the subject's native functional space and used as a mask to extract the timeseries of each seed from the subject's residuals map, still in the subject's native space. Voxel-wise correlations were Fisher-Z-transformed and nonlinearly registered back into standard space. Simple t-tests were then used to determine which voxels were significantly correlated with the seed's timeseries for the ASD and TD groups separately, and independent-samples t-tests were used to determine voxels in which there were significant group differences in correlation with the seed region. Similar procedures were also used to correlate a seed's timeseries with all other voxels in its functional network (network maps from [26]), and to correlate a network's average timeseries with each other network.

Summary of Three Main Results

In each Figure below, orange/red colors = ASD under-connectivity (TD>ASD) and blue/green colors = ASD over-connectivity (ASD > TD).

1. Default Mode Network

Using the posterior cingulate cortex (PCC) seed, a very large cluster (3280 voxels) of under-connectivity in the ASD group was found between PCC and the precuneus (Fig 1). Other smaller clusters were found in bilateral thalamus, bilateral parahippocampal gyrus, anterior vermis, lobule VIII of the left cerebellum and left superior parietal lobule (Fig 2). Clusters of over-connectivity were found in right inferior frontal gyrus (pars opercularis and pars triangularis) and right middle temporal gyrus (Fig 3).

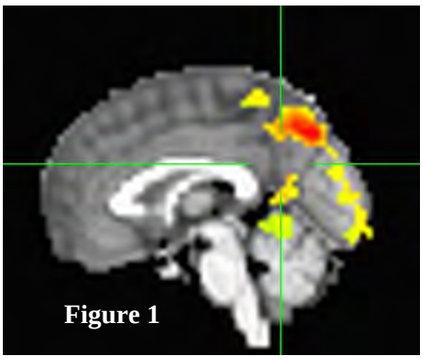


Figure 1

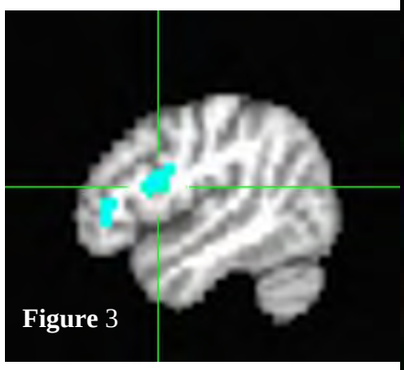


Figure 3

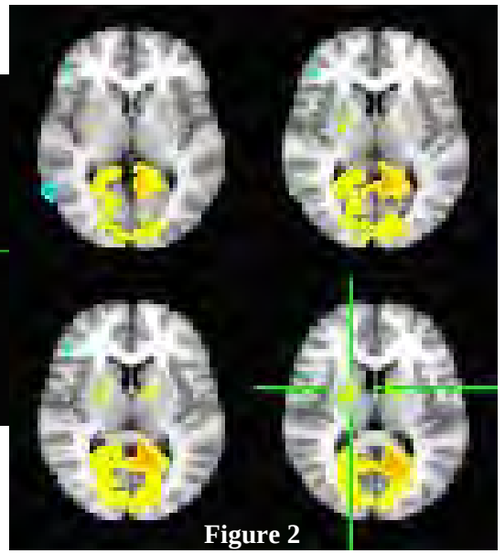
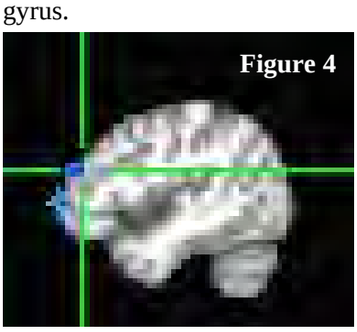


Figure 2

Using a left angular gyrus (AG) seed, small clusters (26-49 voxels) of under-connectivity with the left AG were found in the right precuneus, left uncus,

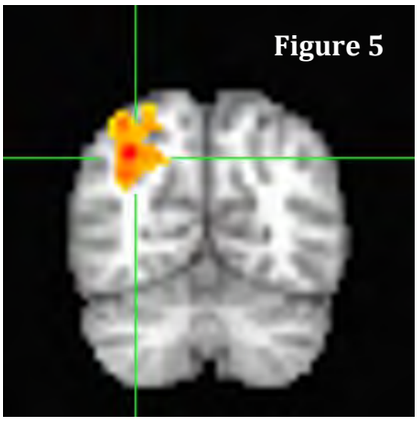
and left inferotemporal pole, while small clusters of over-connectivity were in the left insula, and left inferior temporal gyrus.



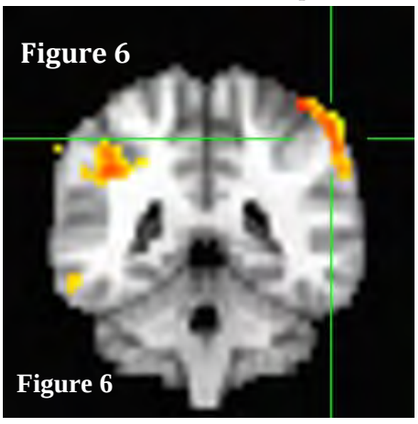
Using the left mesial prefrontal cortex (mPFC), clusters of over-connectivity (32-100 voxels) were observed in the left middle frontal gyrus (Fig 4), left precentral gyrus, right inferior temporal gyrus, and right insula.

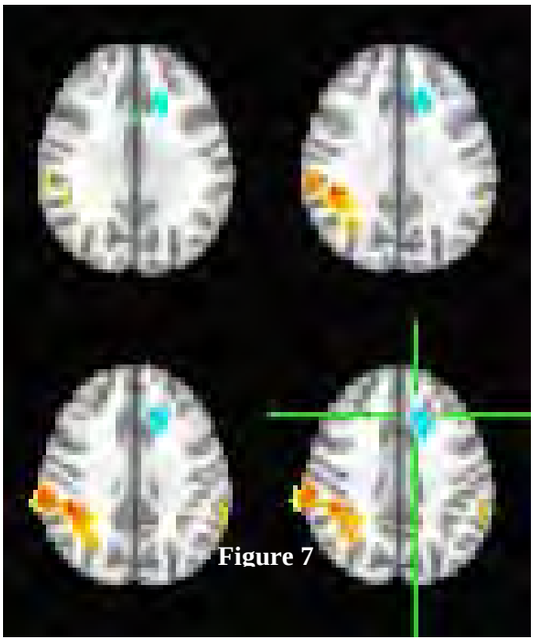
2. Dorsal Attention Network

Using the left middle temporal (MT) gyrus seed, a large cluster (344 voxels) of under-connectivity with the MT seed in the ASD group at a threshold of $p < .01$ was found in the right precuneus region (Fig 5). Other clusters of under-connectivity were found in the left precentral gyrus, right MT, left pallidum, and left IPL.



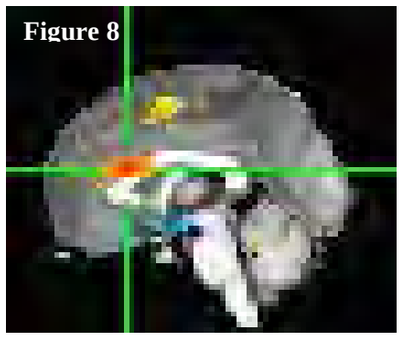
With a left intraparietal sulcus (IPS) seed, a large cluster (469 voxels) of under-inter-hemispheric connectivity in the ASD group at a threshold of $p < .01$ was found in the right IPS (Fig 6). Further clusters of ASD under-connectivity with the left IPS seed were observed in the left inferior parietal lobule, the right superior parietal lobule and the right MT (Fig 7), while clusters of ASD over-connectivity were observed in the left superior frontal gyrus and anterior cingulate (Fig 7).





3. Salience Network

With an anterior cingulate cortex (ACC) seed, very small (27-37 voxels) clusters of under-connectivity were observed in right precentral gyrus, right postcentral gyrus, right middle cingulate gyrus, the left superior temporal gyrus, and left inferotemporal pole.



With a left insula seed, a cluster (171 voxels) of over-connectivity was observed in the right superior temporal gyrus. Other smaller clusters of over-connectivity were seen in orbitofrontal cortex, left calcarine gyrus, and left middle occipital gyrus. A cluster (88 voxels) of under-connectivity was seen in the anterior cingulate cortex (Fig 8), while smaller clusters of under-connectivity were in left supplementary motor area and cerebellar vermis.

Using a right insula seed, a large cluster (441 voxels) of over-connectivity was observed in the right occipital pole. Other over-connected clusters were seen in left superior temporal gyrus, bilateral calcarine gyri, bilateral middle temporal gyri, and left inferior frontal gyrus, while under-connected clusters were in bilateral thalamus and left fusiform gyrus.

4. Final Results To Be Provided To Dr. Glahn In The Coming Months

In the coming months we will be able to provide Dr. Glahn with the final set of these initial intrinsic network results. In addition, we will compare and contrast these initial ASD intrinsic network results to results from Dr. Fox's multi-stage MACM analyses that he will provide in the coming months, and we also will provide our subsequent analyses to Dr. Glahn.

c. What opportunities for training and professional development has the project provided at the UC San Diego Site?

While a major goal of the project at our site was not to provide training and professional opportunities, we nonetheless were able to do so. While we seek a postdoctoral fellow with experience in fMRI analyses of resting state data, we and Dr. Eyler teamed up to get the project moving to meet milestones. She and I have collaborated previously on a variety of ASD neuroimaging studies. Working together, we developed the plan of actions needed to achieve goals and milestones and we trained a new Neuroscience graduate student, Megan Kirchgessner, in my lab on fMRI analyses of resting state data, something that was entirely new to her. Through our training during the first half of this year, Megan has gained substantial proficiency in this state-of-the-field area of neuroimaging methodology as well as knowledge of resting state literature in general and ASD specifically. She interacted with us on a weekly, often daily basis, and gave a lecture on the project and her work to my Autism Center of Excellence at UC San Diego.

d. How were the results disseminated to communities of interest? N/A

e. What do you plan to do during the next reporting period to accomplish the goals?

In the coming year, we anticipate analyses of additional seed locations based on Dr. Fox's meta-analyses connectivity modeling as well as analyses, such as partial least squares (see Courchesne and colleagues, Neuron, April 2015), that could also provide direct brain-clinical behavior relationships and identification of intrinsic network-clinical outcome subtypes in ASD.

4. IMPACT

a. What is the impact on understanding ASD brain development of the project?

Our initial intrinsic connectivity analyses of ASD at the age of first clinical diagnosis provides evidence of significant and widespread disruptions in the functional networks that are crucial for social, communication, cognitive, attention and salience functions (**Section 3. ACCOMPLISHMENTS**, above). These are among the first ever studies of the intrinsic connectivity patterns in infants and toddlers with ASD at the age of first clinical identification.

Although beyond the score of this first summary Report, our current findings are consistent with the ASD literature pointing to prenatal pathology involving excess proliferation[11], mis-migration[15], excess axons[25,27], patches of cortex with disorganized lamina[15] and aberrant synapse formation and function[14,16,28]. Early human connectivity patterns require normal genesis and operation of the subplate during fetal development and multiple lines of evidence suggest its function is abnormal as well[10]. Our intrinsic connectivity results also fit well with very new DTI-based connectivity data on ASD infants that show an excess of aberrantly small axons in multiple cortico-cortical and cortico-subcortical tracts during the

first two years of life[25]; results also show that these axons fail to grow normally. One interpretation is that such tract abnormalities could cause functional connectivity in diverse intrinsic networks.

In this context, it is notable that reports on older ASD children and adults seem to imply that what distinguishes ASD from TD is that ASD individuals maintain idiosyncratic over- and under-connectivity patterns whereas TD connectivity is more canonical [29]. However, not all resting state networks appear to be equally impacted in the autistic brain. For instance, the DMN, but not the DAN, seems to be hypo-connected in adults [30,31] and older children [32] with ASD. However, DMN over-connectivity has been reported in children with ASD ages 7-11 [33]. Although the DMN has received by far the most attention in ASD, the salience network, comprised mainly of the anterior cingulate cortex (ACC) and anterior insula, has also been implicated in ASD. Uddin et al [34] found hyperconnectivity in children with ASD within multiple networks putatively corresponding to salience, posterior DMN, frontotemporal, motor, and primary and association visual networks. The salience network was by far the best classifier of ASD with 78% classification accuracy.

b. What was the impact of the project results on other disciplines, technology transfer, or society beyond science and technology?

Nothing to report at this time.

5. CHANGES/PROBLEMS

No scientific, design or experiment problems have occurred here. We completed pre-processing of MRI structural and fMRI resting state data from large samples of ASD and TD infants and toddlers as planned and we completed an initial set of region-seed based analyses of three intrinsic networks in these N-96 subjects. We are prepared for the next stages of the project.

As described in detail in Section 7. Participants, below, we have encountered problems in finding a post-doc with advanced neuroimaging skills in resting state analyses and in autism.

We solved this problem as described in Section 7 by hiring Dr. Lisa Eyler part-time and training a graduate student, Megan Kirchgessner, to provide important assistance under the supervision of Drs. Courchesne and Eyler. Nonetheless, because much more work is required to complete the next stages of the project, we continue to seek a qualified postdoc or a young faculty person with high expertise in fMRI statistical analyses. Currently three are under consideration by us. Therefore, unexpended funds from the Year 1 Budget will be carried forward to the coming year to bring on either a postdoc or a young faculty person with suitable expertise.

6. PRODUCTS

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name: Dr. Eric Courchesne

Project Role: PI

Research Identifier (e.g. ORCID ID): 0000-0002-3772-5799

Nearest person month worked: 1 cal month

Contribution to project: At the UC San Diego Site, Dr. Eric Courchesne who is Site P.I., Dr. Lisa Eyler and Megan Kirchgessner have worked on the project here. To keep the project goals and milestones on track, Dr. Courchesne decided the best immediate course was to request approval for hiring Dr. Eyler at 10% on the grant because she has expertise in fMRI methodology and autism neuroimaging and has been a reliable collaborator in the past. She and Dr. Courchesne advanced the projects goals and milestone successfully as seen in the Report above. In addition, Dr. Courchesne recruited a Neuroscience graduate student, Megan Kirchgessner, to assist, and we trained her as mentioned above and she has played a valuable role. Nonetheless, as we write in Section 5 above, “because much more work is required to complete the project and results suggest that additional advanced analyses to seek subtypes of intrinsic network pathology in ASD be implemented, we continue to seek a qualified postdoc or a young faculty person with high expertise in fMRI statistical analyses. Currently three are under consideration by us. Therefore, unexpended funds from the Year 1 Budget will be carried forward to the coming year.”

Funding Support:

Progenity, Inc.
NIH/NIMH R01 MH104446
NIH/NIMH R01 MH076431
CIRM

Name: Lisa Eyler

Project Role: collaborator

Research Identifier (e.g. ORCID ID): 0000-0002-7783-8798

Nearest person month worked: 1 cal month

Contribution to project: Dr. Eyler has expertise in fMRI methodology and autism neuroimaging and has been a reliable collaborator in the past. She and Dr. Courchesne advanced the projects goals and milestone successfully as seen in the Report above.

Funding Support:

NIH/NIMH R01 MH083968
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NIH/NIA R01 AG049369
NIH/NIA R01 AG022381

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

As per the original application, the other organizations involved as partners are the University of Texas (Dr. Fox, the overall Project P.I.) and Yale University (Dr. Glahn, PI at that Site).

8. SPECIAL REPORTING REQUIREMENTS

This is part of a Collaborative Award and this Progress Report is from the UC San Diego Site (Courchesne).

9. APPENDICES

See REFERENCES, below.

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